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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,112	12/26/2001	Andre Rosowsky	48460(70157)	5913

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,112	ROSOWSKY, ANDRE	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3 and 4* is/are allowed.

6)☒ Claim(s) *1,5-8 and 11-34* is/are rejected.

7)☒ Claim(s) *9 and 10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is in response to amendments filed on 6/30/03. Applicant has amended claims 1, 3-8, 10-26. Claims 27-34 are new. Applicant has cancelled claim 2. There are thirty-three claims pending and under consideration. Claims 1 and 3-10 are compound claims. Claim 26 is a composition claim. Claims 11-15 and 27-34 are use claims. This is the second action on the merits. The application concerns some dibenazepine compounds, compositions, and uses thereof.

Response to Amendment

2. Applicant's amendment to the claims limiting the subject matter overcomes the objection made in point #5. Applicants new abstract overcomes the objection made in point #6. This abstract does not contain a formula of the claimed compounds but is otherwise satisfactory. There is a change in USPTO practice concerning non-standard usage of art-recognized terms. Thus, both the objection made in point #7 and the indefiniteness rejection made in point #13 are withdrawn. Applicants amended title and correction of the claim dependency overcomes the objections made in points #8 and #9. Applicant's argument concerning the substituents is persuasive and the indefiniteness rejection made in point #10 is withdrawn. Applicant's deletion of preferably overcomes the indefiniteness rejection made in point #12. Applicant's addition of the missing terms overcomes the rejections made in points #15 and #16. Applicant's amendment to claim 17

makes clear that no crystal ball is needed and overcomes the rejection made in point #18. Applicant's amendment, requiring an amino substituent on the heteroaryl ring of variable Ar overcomes the anticipation rejections of Mueslin (CH 372,675), Marangos (Eur. J. Pharm.), Kihara ('200), Andrreani (Eur. J. Med. Chem.), Ohshima (EP 549,352 A), Garforth (J. Enzyme Inhibition), Takami (JP 8/119,920), and Beilstein (Ref AG) made in points #19-26. Applicant's addition of the missing requirement that the malaria treatment be performed with Applicant's claimed compounds overcomes the art rejections made in points #27 and #28.

3. Applicant is employing a nonstandard definition of the common chemical terms alkyl and alkenyl. On page 8 alkyl groups are defined as "refers to both cyclic or noncyclic groups". Neither alkane nor alkene hydrocarbons are normally cyclic. However, Applicant has clearly set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. This meets the standards provided by *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The Examiner suggests that the definition of alkyl from the specification be placed into the claims 1 and 3-7 so that the public will not be forced to pour through the specification to understand Applicant's special meaning of the terms.

Claim Objections

4. Objection remains to claim 26 to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

Applicants corrected the problem in all other claims but not claim 26.

Claim Rejections - 35 USC § 112

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1, 5-8, and 11-26 remain rejected and claims 27-34 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1 and 5-7, in the definition of variable W, Applicant uses the limitation "having 1 to about 3 carbon atoms". This is indefinite because the word "about" fails to clearly delineate Applicant's invention. Since atoms occur only in whole units, we understand that 2.9 or 3.1 carbon atoms are not intended. However does "about 3 carbon atoms" mean 3 or could it be 4? Could Applicant intend this to mean at most 2?

The Examiner suggests removing the word "about".

Applicants state in their remarks that the claims have been amended to overcome the rejection. However, the word "about" still appears in claims 1 and 5-7.

6. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Variables T, U, and V may be "optionally substituted nitrogen", yet in Formula III all three atoms have three required bonds. Nitrogen is a trivalent atom. In a six-membered ring it is not chemically possible for a nitrogen atom to have an external substituent.

The Examiner suggests removing "optionally substituted" concerning nitrogen.

Applicants make three arguments. Firstly they dispute that nitrogen is trivalent. Secondly, they suggest that an N-oxide could be the optional fourth substituent. Thirdly, they suggest that pyridinium salts could be the optional substituent. This is not persuasive. The word valence refers to the number of bonds formed to other atoms, not to the number of electron pairs possessed by an atom. Both boron and nitrogen are trivalent as exemplified by the compounds BCl_3 and NCl_3. Boron has three electron pairs in its' outer most shell but nitrogen has four. Oxygen is divalent as exemplified by water but has four electron pairs in its' outer most shell. The valence is not equal to the number of electron pairs. FYI, the hybridization of the nitrogen atom in a pyridine ring is sp^2 not sp^3. Secondly, substituted refers to the process of removing an atom, normally hydrogen, and

replacing it by another radical. What atom is removed in the process of oxidizing pyridine to pyridine N-oxide? Where in the specification is the possibility of such oxides mentioned? Such an oxide is not "substituted". Thirdly, what counter ion do Applicants intend for their hypothetical pyridinium salts? Where is this counter ion taught or, for that matter, the possibility that immonium salts are intended? Again, what atom was removed from pyridine to make the pyridinium salt?

7. Claims 11-25 remain rejected and claims 27-33 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating patients suffering from diseases, does not reasonably provide enablement for treating patients "susceptible to a" disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The only established prophylactics are vaccines not the dibenazepine compounds such as present here. It is presumed that prevention of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. All people are susceptible to parasitic diseases.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before parasitic infection occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The paragraph spanning page 16 to page 17 lists the diseases Applicant intend to treat. In the final two sentences there is a discussion of AIDS and cancer patients. Are these the only patients "susceptible to a" infection, or are there others? 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical infective medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become infected by parasites before the fact. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of parasitic diseases generally. Under

such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. 6) The artisan using Applicants invention would be a Board Certified physician in infectious diseases or tropical medicine with an MD degree and several years of experience. The failure of skilled scientists to achieve the goal of preventing all parasitic infections is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent infections by parasites generally. That is, the skill is so low that no compound effective generally against parasitic disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8) The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases. The term parasitic disease is a general category that arises from dissimilar organisms related only by a shared behavior. This is a very diverse set of creatures with nothing in common biochemically or morphologically. Most of these parasites do not rely

upon the dihydrofolate reductase enzyme which is found in malaria parasites and which is described in the *in vitro* assay in lines 4-12, page 37 of the specification. Even if Applicant's compounds could prevent malaria, there is no reason to believe that infection by other parasites lacking this enzyme could be prevented. Additionally, the claims read on the multitude of compounds embraced by Formula I. Thus, the claims are extremely broad.

The Examiner suggests deletion of the phrase "susceptible to a".

Applicants point to lines 16-25, page 6 and the paragraph spanning line 26, page 16 to line 4, page 17 as clarifying which people are susceptible to parasitic infections. Applicants argue that those susceptible are the AIDS and cancer patients discussed above. This is not persuasive because the passages cited use open language, "include", may suffer", and "for instance". Who in addition to AIDS and cancer patients are to be included? All humans are susceptible to parasitic disease. No one has a magic barrier that makes him or her impervious to infection. Not everyone traveling to Africa develops schistosomiasis, for example, it depends upon the exposure. Furthermore, not everyone exposed to the five infective schistosomes develops symptoms of schistosomiasis. It is unclear why two people exposed to the same parasitic challenge do not have the same probability of becoming diseased. While schistosomiasis, leprosy, and elephantiasis are more common in tropical countries, our incidence in the US is

low, because our water is clean. That does not change the fact that we are all susceptible. The parasitic diseases amoebic dysentery, malaria, and cercarial dermatitis are found in the US. Water born amoebic dysentery puts every one who drinks water at risk. While infrequent, infections appear to occur worldwide. The free-living amebas belonging to the genera *Acanthamoeba*, *Balamuthia*, and *Naegleria* are important causes of disease in humans and animals. *Naegleria fowleri* and *Acanthamoeba spp.*, are commonly found in lakes, swimming pools, tap water, and heating and air conditioning units. Anyone swimming in a lake, ocean beach, or pool anywhere in the world is at some risk. Cercarial dermatitis occurs worldwide with cases reported from every continent except Antarctica. In the United States, cases are commonly reported from the Great Lakes region. Last summer malarial infections occurred in Fairfax County, Virginia. Who knew all patent examiners were at risk? *Toxoplasma gondii*, the subject of claim 19 has very low host specificity, and it will probably infect almost any mammal. It has also been reported from birds, and has been found in virtually every country of the world. *Toxoplasma gondii* can be transmitted transplacentally resulting in a spontaneous abortion, a stillborn, or a child that is severely handicapped mentally and/or physically. Thus, every new born is at some risk for this parasitic disease. Thus, identification of those susceptible to a parasitic disease is not an easy task.

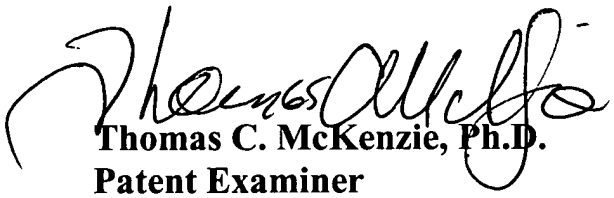
Allowable Subject Matter

8. Claims 3 and 4 are allowed. Claims 9 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in

independent form including all of the limitations of the base claim and any intervening claims. Claims 1, 5-8, and 26 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action.

Conclusion

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.



Thomas C. McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK